TB MED 72

WAR DEPARTMENT TECHNICAL BULLETIN

TREATMENT OF CLINICAL MALARIA AND MALARIAL PARASITEMIA

War Department, Washington 25, D. C. . . . . 10 July 1944

This bulletin supersedes S. G. O. Circular Letter No. 153, 19 August 1943, except paragraph 4; and S. G. O. Circular Letter No. 197, 27 December 1943, which are hereby rescinded. Paragraph 4, S. G. O. Circular Letter No. 153, was superseded by TB MED 65, 3 July 1944

1. DIAGNOSIS. *a. General.* Malaria causes symptoms which mimic a wide range of diseases. It should be suspected not only in patients with periodic chills and fevers, but also in any obscure illness, with or without fever, in endemic regions and in personnel who have served in endemic regions. Among troops who recently have been taking suppressive medication, the classical picture of regular chills and fever is not frequently seen. The triad of headache, backache, and fever, with or without chills, is the commonest symptom-complex in these individuals. Furthermore, in recently exposed persons, delirium, coma, or medical shock should immediately suggest the possibility of malaria. Even in severe cases, the temperature may be subnormal. In summary, wherever the possibility of malaria exists, the diagnosis should be considered no matter what clinical picture is presented.

b. Laboratory diagnosis. When competent examination of the blood is possible, antimalarial chemotherapy should be given only in cases in which the malarial parasite has been found or in cases of urgent illness which admit of no delay. The habitual administration of atabrine or quinine in all fevers in a malarious area, before demonstration of the parasite, is a dangerous practice. Repeatedly negative thick blood films cast a doubt on a diagnosis of clinical malaria and should lead to close observation to determine whether the etiology is other than malaria.

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(1) *Blood films.* Thick smears should be examined as soon as possible, each being studied for at least 5 minutes before being declared negative. If parasites are not found, smears should be made at intervals of less than 24 hours for several successive days, since the symptoms of a first attack may appear when the density of parasites is low and since in *falciparum* infections there may be very few parasites in the blood during the second 24 hours of the asexual cycle. In heavy *falciparum* infections, the proportion of infected red cells should be estimated. Thin smears also should be made for use when the species of parasite cannot be determined from the thick smear. If thin smears alone are used for diagnosis, each smear should be studied for at least 10 minutes before being declared negative.

(2) *Verification of technical proficiency.* The accurate diagnosis of malaria by thick or thin smears requires prolonged experience. Mistaking blood platelets for plasmodia is the commonest error. In the Tropics, the growth of molds and bacteria in stains is a frequent source of confusion. The reliability of the work of technicians should be constantly checked by a competent laboratory officer.

c. Importance of species diagnosis. Effort always should be made to determine what species of parasite is present. The diagnosis of *falciparum* malaria calls for close observation of the patient for the onset of dangerous symptoms; repeated relapses are unlikely. In contrast, *vivax* malaria is not likely to become suddenly dangerous, but repeated relapses are common.

d. Treatment without demonstration of parasite. Military operations, lack of laboratory facilities, or clinical urgency may make it necessary to give antimalarial treatment without laboratory confirmation of the diagnosis. Blood films should be taken, when possible, for later study. In such cases, keen observation is essential in order to discover cases of meningitis, pneumonia, or other febrile disease, which may simulate and may be assumed mistakenly to be malaria.

2. CHOICE OF DRUG. *a. Atabrine (quinacrine hydrochloride, USP, mepacrine in British usage).* The experience of the Army and Navy in the last 2 years thoroughly demonstrates that atabrine is as effective as quinine and indicates that in many respects it is to be preferred. Dosages of atabrine formerly in use were significantly slower than quinine in producing a clinical response; administration of larger initial doses has overcome this disadvantage. Atabrine has been shown to be curative (in the strict sense of the word) of a high proportion of *falciparum* infections. The action of quinine in this regard is uncertain at present. Extensive experience indicates that atabrine in recommended doses is associated with fewer and less troublesome untoward symptoms than quinine. Atabrine, therefore, is the drug of choice for the treatment of clinical malaria in general.

b. Quinine. The intravenous use of quinine is indicated in patients critically ill with malaria. Since the available supply of quinine is strictly limited, the drug must not be used for routine oral medication. Its use by mouth should be restricted to occasions on which atabrine is not available, instances of serious intolerance to atabrine, and selected cases in which repeated relapses have occurred following courses of atabrine, when a change of drug is considered highly desirable. The use of quinine for study purposes is restricted to plans approved by competent authority (in the United States, by The Surgeon General; overseas, by the theater surgeon).

c. Totaquine. This combination of cinchona alkaloids has an action which closely parallels that of quinine. It can be given only by mouth. Totaquine is available for use in selected cases in fixed medical installations. It should not be used in severe cases, especially those due to *falciparum* infections, unless atabrine and quinine are not available. Because of the greater efficacy of atabrine in certain regards (see *a* above and paragraph 11) and because of the frequency of gastro-intestinal disturbances following totaquine, this preparation should not be used in forward areas.

d. Plasmochin. This drug is useless as the sole antimalarial for therapy. It was formerly recommended for use in combination with quinine or following a course of atabrine. The therapeutically effective and seriously toxic doses of plasmochin are separated by a rela-

tively small margin. Army experience shows no detectable effect on the subsequent incidence of *vivax* relapse. The destruction of gametocytes by plasmochin has not been shown to be a practicable means of controlling the spread of malaria. The use of plasmochin for this purpose in Army personnel in highly endemic regions where natives are not treated would be futile. Plasmochin, therefore, should not be used routinely. When gametocytes persist after routine treatment, a course of plasmochin may be added.

e. Arsenical and bismuth preparations. Available evidence indicates that neoarsphenamine, mapharsen, and certain preparations of bismuth, are effective in clinical attacks of *vivax* malaria, but that, like atabrine and quinine, they do not prevent the subsequent occurrence of *vivax* relapses. Following treatment with these preparations, *vivax* relapses often occur after a very short interval. Treatment with neoarsphenamine or mapharsen must be regarded as potentially more dangerous than *vivax* malaria when properly treated with atabrine or quinine. *These drugs cannot be relied upon to control clinical attacks due to falciparum infections.* Since they present certain serious disadvantages and no known advantage in comparison with atabrine, quinine, or totaquine, the arsenical and bismuth preparations in question should not be used in the treatment of malaria, except when atabrine, quinine, and totaquine are not available.

f. Penicillin. This drug has been found to have no influence on parasitemia or clinical symptoms of malaria.

3. UNTOWARD EFFECTS OF ANTIMALARIAL DRUGS. All available drugs may give rise to toxic reactions. A few individuals are seriously intolerant of each.

a. Atabrine. Untoward effects of any type are unusual when atabrine is used for the treatment of clinical malaria. Symptoms, such as nausea, vomiting, abdominal cramps, diarrhea, and headache, which occur in some normal individuals when they first take atabrine as a suppressive drug, are uncommon in association with clinical treatment. Such symptoms, especially early in the treatment, are then more apt to be due to the disease itself. No evidence of damage to the liver by clinical treatment with atabrine has been reported. Mild excitement occurs in a small percentage of patients treated with atabrine; in rare cases, acute delirium has been attributed to the drug. Such reactions are indistinguishable from those occasionally associated with many other drugs. They are said to appear more frequently in individuals with a psychopathic background and with very large doses, such as 4 grams or more in a week. They disappear rapidly when the use of the drug is discontinued. Skin rashes and other allergic manifestations rarely occur; in such cases, quinine or totaquine should be immediately substituted for atabrine. Atabrine is a yellow dye. Its staining of the skin bears no relation to any toxic effect. The sclera, although not usually stained, is occasionally colored by atabrine. This pigmentation must not be confused with jaundice. It disappears within a few weeks after the drug is stopped.

b. Quinine. As with atabrine, the administration of quinine leads to few serious untoward effects. Adequate therapeutic dosage, however, is usually accompanied by one or more of the symptoms of cinchonism, viz, tinnitus, dizziness, deafness, tremor, and palpitation. These milder symptoms indicate effective blood levels, but are objectionable to many patients. Very large doses of quinine may cause more serious intoxication. Amblyopia is a rare but dangerous occurrence. Prolonged use of the drug is said to cause rare cases of permanent impairment of hearing. True sensitivity to quinine is more common than to atabrine and may be present in dangerously high degree. Any patient with a history suggestive of an allergic reaction to quinine should be treated with atabrine.

c. Totaquine. This preparation causes much the same untoward symptoms as quinine, but gastrointestinal disturbances, including nausea, vomiting, and abdominal pain, are more frequent and more severe than they are following quinine.

d. Plasmochin. In therapeutically effective dosage, this drug is frequently associated with toxic manifestations. The symptoms include abdominal pain, nausea, vomiting, headache, dizziness, and drowsiness. Hemoglobinuria,

cyanosis and circulatory collapse, jaundice, and acute yellow atrophy of the liver are rare, but exceedingly dangerous effects.

4. RECOMMENDED TREATMENT FOR CLINICAL MALARIA. *a. Uncomplicated malaria (patient able to retain oral medication) and parasitemia without symptoms.* Atabrine dihydrochloride (quinacrine hydrochloride USP) 0.2 gram (3 grains) and sodium bicarbonate 1 gram (15 grains) by mouth with 200 to 300 cc of water (or an equal amount of sweetened tea or fruit juice) every 6 hours for five doses, followed by atabrine 0.1 gram (1½ grains) three times a day after meals for 6 days (total 2.8 grams in 7 days).

b. Malaria with persistent vomiting, coma, impending coma, or high density of falciparum parasites in blood smears (5 percent or more of red cells infected). In these cases, and whenever a patient cannot retain or fails to respond to oral medication, even though he may not appear critically ill, atabrine should be given intramuscularly or quinine should be given intravenously. Atabrine by the intramuscular route is also recommended for patients with serious complicating diseases, such as dysentery, pneumonia, meningitis, or grave injuries.

(1) Atabrine dihydrochloride 0.2 gram (3 grains) in 5 cc sterile distilled water injected *intramuscularly* into each buttock (total 0.4 gram or 6 grains), with the usual precautions. Massage is unnecessary and undesirable. Effective plasma concentrations are attained in 15 minutes; and maintained for about 6 hours. If necessary, one or two additional doses of 0.2 gram (3 grains) may be given intramuscularly at intervals of 6 to 8 hours. As soon as the patient can take and retain oral medication, atabrine should be given by mouth in such doses as to give a total by both routes together of 1.3 grams in 48 hours, followed by 0.1 gram three times a day after meals for 5 days (total 2.8 grams in 7 days).

(2) Quinine dihydrochloride 0.6 gram (10 grains) in sterile physiological saline 300 to 400 cc (minimum 200 cc) injected *intravenously* with the usual precautions, especially avoiding speed. If necessary, there should be no hesitation to cut down to the vein. The drug is almost immediately effective, but is eliminated in about 3 hours. This treatment may be repeated in 3 to 4 hours, if necessary, but it is preferable to anticipate the need by the intramuscular injection of atabrine immediately following the intravenous administration of quinine. As soon as the patient can take and retain oral medication, a complete course of atabrine should be given, as described in *a* above (taking into account any intramuscular doses of atabrine; the total amount should be 2.8 grams in 7 days).

5. ALTERNATIVE TREATMENT PLANS. The methods of treatment described in paragraph 4 are satisfactory in nearly all cases. In the hope of lessening the incidence of relapses, almost every conceivable variation in the use of available drugs has been tried during the recent past. Such variations have embraced increased dosage, prolongation of administration, and many combinations of drugs, without demonstrating significantly increased efficacy over the recommended treatment. By and large, more satisfactory results in the therapy of clinical malaria are secured by general adherence to a simple, well tested plan, than by frequent modifications which seldom have a sound basis. Deviations from the recommended plans, therefore, should be limited to cases in which there are well-defined indications.

a. Quinine by mouth. See paragraph 2*b*; note that the use of quinine by mouth is officially limited as described therein. Dosage: Quinine sulfate 1 gram (15 grains) three times a day after meals for 2 days, followed by 0.6 gram (10 grains) three time a day after meals for 5 days (total 16 grams in 7 days).

b. Totaquine. See paragraph 2*c*, where the field of possible usefulness and the limitations of this drug are described. Dosage: Totaquine USP 1 gram (15 grains) three times a day after meals for 2 days, followed by 0.6 gram (10 grains) three times a day after meals for 5 days (total 16 grams in 7 days).

c. Plasmochin. See paragraph 2*d*. Plasmochin should be given only under careful medical supervision. It should not be given to debilitated patients. The dosage stated below should not be exceeded. Plasmochin may be given immediately following, but not together with, atabrine; or it may be given during the last days

of a course of quinine. Discontinue plasmochin at once, if any toxic symptoms appear. Dosage: Plasmochin naphthoate (pamaquine naphthoate, USP) 0.02 gram (⅓ grain) and sodium bicarbonate 1 gram (15 grains) by mouth three times a day after meals for 4 days. The fluid and sugar intake should be liberal during and for some days after the course. (Note that the dose of plasmochin naphthoate, 0.02 gram, is the equivalent of the dose of 0.01 gram formerly recommended which was in terms of plasmochin hydrochloride.)

6. GENERAL CARE. *a.* In places where anopheline mosquitoes may be present, the patient should be kept in bed in a screened ward or under a mosquito bed-net (with care that he does not sleep against the net).

b. The fluid intake should be maintained at 3 to 4 liters per 24 hours, using the intravenous route if necessary. Sweetened tea and fruit juices are usually well accepted. If sweating is, or has been profuse, the sodium chloride balance should be restored and maintained by giving supplementary amounts of salt. Chills may be relieved by hot water bags and blankets, and high fever by cold sponges and packs. Antipyretics are contraindicated. If a sedative is necessary, one of the barbiturates should be used judiciously.

c. When nausea or vomiting is present, the intake of solid food should be stopped, particularly when a febrile paroxysm is expected. Sips of alkaline water may help. If vomiting is frequent, 5 percent glucose in physiological saline solution, with 1 mgm. thiamine hydrochloride for each 25 grams of glucose, should be injected intravenously. From 200 to 400 cc may be injected by the usual technique, with repetition as necessary. If desired, the solution may be given by the continuous drip method.

d. Convalescence from uncomplicated isolated attacks of malaria is usually rapid, ordinarily not more than 10 to 14 days. Such patients should not be kept in hospital unduly long. Patients who have had many attacks of malaria, especially when the intervening intervals are short, may remain for an excessively long time in a debilitated and depressed state. Patients who have injuries or other diseases often fall in this group. In such cases, full use should be made of available measures to hasten recovery, including—

(1) Diets which are liberal and well planned both as to nutritive value and as to attractiveness and palatability.

(2) Vitamin supplements.

(3) Iron replacement, if anemia is present (ferrous sulfate grains 10 three times a day after meals).

(4) Physical therapy in suitable forms.

(5) Adequate rest and sleep, with judicious use of sedatives.

(6) In selected cases, suppressive antimalarial medication, as described in paragraph 8.

(7) As soon as possible, the patient should enter a reconditioning program.

7. PRACTICAL POINTS IN MANAGEMENT OF MALARIA. *a. Regarding diagnosis.* (1) Previous diagnosis should not be allowed to mislead the observer. Malaria should be suspected whenever the possibility exists, no matter what symptoms and signs exist. Clinical attacks often occur 3 to 4 weeks and sometimes many months after discontinuing suppressive treatment.

(2) Repeated thick film studies by competent technicians are essential. With very few exceptions, the first or second examination shows parasites in cases of malaria. Parasites are generally more numerous in relapses than in primary attacks, especially in *falciparum* infections. The prior use of suppressive treatment does not appear to reduce significantly the chance of finding parasites in thick films. The symptoms and signs of illness in a patient whose thick blood films are repeatedly negative over a period of several days are almost surely not due to malaria. Other important possibilities should be considered. Dengue and sand-fly fever, among other diseases, have given rise to confusion in forward areas.

(3) The therapeutic test with atabrine, or especially quinine, must be interpreted with great caution, since these drugs are not exclusively specific in their effects. Furthermore, febrile diseases with short, self-limited courses, such as dengue and sand-fly fever, often cause confusion.

(4) Even when malaria parasites are present in blood films, the patient may not be suffering from clinical malaria and another disease may be present, for which specific treatment may be necessary.

(5) Blood films are positive in only a negligible proportion of cases of latent malaria. Hence, negative smears do not exclude the presence of a latent infection or the subsequent occurrence of a relapse. None of the occasionally provocative measures, such as the injection of epinephrine or of typhoid vaccine, can be relied on to produce parasitemia in all latent cases; such measures should not be used routinely.

b. Concerning medication. (1) The recommended treatment is in general equally effective in infections with any species of malarial parasite and in relapses as well as in primary attacks.

(2) The prior administration of suppressive treatment does not affect the choice of drug for clinical treatment. There is no evidence that parasites become resistant to any of the antimalarial drugs.

(3) In all cases of oral medication, the taking of each dose should be closely supervised, since patients, even in clinical attacks, occasionally attempt to evade drug treatment in whole or in part. Both atabrine and quinine are readily absorbed as a rule, although tablets occasionally may pass unchanged through the gastrointestinal tract. When a patient diagnosed as having malaria by blood film fails to respond to oral medication, he should be treated perenterally.

(4) Under military stress in forward areas, the period of treatment recommended in paragraph 4*a* may be shortened by giving atabrine 0.2 gram (3 grains) three times a day after meals on the second, third, and fourth days (total 2 8 grams in 4 days). This compression of treatment is not recommended for use under other circumstances.

(5) If parasitemia persists after a course of treatment described in paragraph 4, 5*a* or 5*b*, medication should be prolonged at the "maintenance" rate until the total period of treatment is 3 weeks (maintenance dose for atabrine 0.1 gram three times a day; for quinine and totaquine 0.6 gram three times a day.)

(6) A patient with parasitemia but no clinical symptoms who has not had a course of treatment within 2 weeks, should be hospitalized and given treatment as recommended in paragraph 4*a*. When *falciparum* parasites are present in such cases, treatment should always be instituted at once. If for any reason, treatment is postponed in other cases, the patient must be kept in hospital under close medical surveillance and protected from mosquitoes, until thick blood films have been negative on two occasions, 2 days apart.

(7) The course of treatment, described in paragraphs 4 and 5, should not be repeated until an interval of 2 weeks has elapsed.

(8) In the absence of parasitemia or clinical symptoms, there is no evidence that treatment with any known antimalarial drug influences the future occurrence of relapses. Therefore, patients who are free of symptoms and whose blood films fail to show parasites should not be treated, except as described in paragraph 8.

8. SUPPRESSIVE MEDICATION IN MANAGEMENT OF KNOWN CASES OF VIVAX MALARIA. As a rule, clinical relapses of *vivax* malaria may be prevented by the regular daily administration of small doses of atabrine. Overseas, suppressive medication has been employed successfully in units known to be heavily infected with malaria in order to maintain military effectiveness. Recommendations concerning the routine use of drug suppressive treatment apart from diagnosed malaria are given in TB MED 65, 3 July 1944. Such treatment is also recommended for use in individual soldiers, under certain circumstances. The purpose of suppressive medication in this connection is therapy in the broad sense. In the United States, this form of suppressive medication is limited to selected individuals or groups of individuals who are known to have *vivax* malaria with laboratory confirmation at a recent date. Overseas, such medication will be employed as theater surgeons may direct.

a. Indications. (1) To permit officers or enlisted men in the status of patients whose general health has suffered seriously from repeated attacks of malaria, or who are under treatment for injuries or other diseases than malaria, to regain their normal health. In selected cases,

suppressive medication may be given during leave of absence, furlough, or sick leave.

(2) To permit individuals with history of frequent relapses to be reconditioned and retrained.

(3) To permit commissioned officers and warrant officers in a duty status to fulfill missions or accept important assignments outside the United States.

b. Precautions. Individuals given suppressive medication should receive thorough indoctrination in the need for regularity in taking atabrine. In order that they may not develop a false sense of permanent security, they should understand that further attacks of malaria will not necessarily be prevented from occurring after they cease to take the drug.

c. Dosage. Atabrine 0.1 gram (1½ grains) every day after a meal (preferably the evening meal), with at least one full glass of water. In rare instances of serious intolerance for atabrine, quinine sulfate 0.6 gram (10 grains) every day may be substituted for atabrine. The period of suppressive medication for this purpose may extend to 3 months or more.

9. RECORDS, FOLLOW-UP. In order to accumulate information which will be of value in determining the efficacy of treatment plans and in increasing our knowledge of the course of malaria, data should be recorded in the clinical record showing the whole course of the patient's malarial history. Only by means of information which is continuous can the need of prolonged follow-up be met. The following points are illustrative of basic data which are required:

a. Previous history. (1) Dates of first entry into endemic region and of any subsequent return to an endemic area.

(2) Suppressive treatment at various times: dates, drug, doses, regularity, intermissions.

(3) Clinical attacks: dates; interval following cessation of suppressive treatment; breakthrough during suppressive treatment; courses of clinical treatment in detail; duration of symptoms; intervals between relapses.

(4) Date of removal from endemic area.

(5) Date of arrival in continental United States.

b. Current attack or relapse. (1) Diagnosis by smear, including malarial species.

(2) Dates of beginning of symptoms, institution of treatment, and cessation of fever.

(3) Rate of disappearance of parasites and date of their final disappearance.

(4) Full clinical notes, including symptomatology and exact plan of drug administration.

c. Postmortem examinations. When a death presumably due to malaria occurs, steps should be taken to confirm the diagnosis. The following items are of special importance:

(1) The gross appearance of the liver, spleen, and brain.

(2) Thin smears of bone marrow, spleen, liver, and brain tissue, fixed in methyl alcohol and stained with Giemsa's stain.

(3) Tissue blocks for sectioning, fixed in Zenker's solution for 8 to 10 hours, washed in several changes of water or in running water for about 6 hours, and preserved in 70 percent ethyl alcohol to which tincture of iodine has been added in sufficient amount to give a straw color.

10. DISPOSITION OF PATIENTS WITH MALARIA. *a.* Uncomplicated malaria alone is not a cause for disqualification for oversea service, except that enlisted men who have or have had a clinical attack of malaria or in whose blood malaria parasites are found will not be sent overseas until a date 6 months subsequent to that of recovery from symptoms or of disappearance of parasites from the blood. In the case of commissioned officers and warrant officers, oversea service at an earlier date is rendered possible by the use of suppressive medication, as described in paragraph 8.

b. Uncomplicated malaria alone or repeated relapse of malaria alone is not a cause of evacuation to the zone of interior or for separation from the service.

c. No patient with malarial parasitemia should be given furlough, sick leave, or be returned to duty, or discharged from the service. The minimum requirement for such action is that the patient should be free of clinical symptoms and that two thick blood films at 2-day intervals should be negative.

d. Before a patient with a history of malaria is granted furlough or sick leave, or returned

to duty or discharged from the service, he should be warned that he may be liable to a recurrence at some future time and that he should have a blood examination for malaria parasites in case of any febrile illness.

11. NOTE ON COURSE OF MALARIA. In Army experience, fatalities directly resulting from any type of malaria have been rare. *Falciparum* infections have relatively little tendency to relapse in comparison with *vivax* malaria (*vivax* infections due to sporozoites transmitted by mosquito bites must be distinguished from those induced by the injection of trophozoite-containing blood; the latter do not relapse). *Vivax* infections relapse as time goes on in a decreasing proportion of the original group. Whereas second attacks may occur in 60 percent or more of those infected, tenth attacks probably affect only 1 percent or less. The interval between attacks tends to be about 4 to 6 weeks, but may be shorter or much longer. In general, later attacks tend to be briefer and milder than early attacks, but there are many exceptions. There is no evidence that climate influences the frequency of relapses, except that one relapse may be precipitated whenever there is any marked change in climate. No criterion of cure is available. As a rough approximation, it may be said that when 6 months have passed without an attack, the further occurrence of numerous relapses is unlikely. Attacks after 2 to 3 years are believed to be unusual.

12. NOTE ON ACTION OF ATABRINE AND QUININE. *a. Absorption and plasma level.* Both of these drugs are rapidly absorbed from the gastrointestinal tract; under ordinary conditions the rates of absorption are not significantly different. Their efficacy is dependent upon their concentration in the circulating blood plasma. The effective plasma level of atabrine is very much lower than that of quinine. Quinine is taken up by the tissues to a smaller extent than atabrine and effective plasma concentrations, therefore, are usually attained promptly. Atabrine at first is taken up to a much greater extent by the tissues, so that efficient levels in the plasma are reached only as certain tissues become more or less saturated. The method of administering atabrine which is recommended in paragraph 4*a*, includes a relatively large amount in the first 24 hours which acts as a "loading" or "priming" dose. By this means, a therapeutic effect may be secured as rapidly with atabrine as with quinine, when both drugs are given by mouth. This method has been used extensively and has proved itself to be highly satisfactory in the treatment of the vast majority of acute attacks.

b. Duration of effect. The elimination of any dosage of quinine is practically complete in 48 hours. After a therapeutic course of atabrine, elimination may not be complete for several weeks. During the latter part of this time, however, the plasma level is far below the threshold of therapeutic efficacy. Nevertheless, an effective level is often maintained for at least 3 weeks. In relapsing *vivax* malaria, it has been shown that the average interval between attacks is significantly longer following a course of atabrine than it is after quinine.

c. Relation to parasite. Available evidence shows that atabrine often cures *falciparum* infections. Whether or not quinine also does, is uncertain. Both atabrine and quinine rapidly bring about the destruction of *vivax* trophozoites. Neither of these drugs can be shown to have any influence on the subsequent occurrence of relapses in *vivax* malaria. It would appear probable that a form of the *vivax* parasite, intermediate between sporozoite and trophozoite, which is not susceptible to atabrine or quinine, exists. The persistence of such forms would be an adequate explanation of the occurrence of *vivax* relapses.

[A. G. 300.5 (15 Jul 44).]

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For explanation of symbols, see FM 21–6.

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